REMARKS

Claims 120-123, 125-126, 128, 130-133, 135-136 and 138 remain pending in the application. Applicants reserve the option to further prosecute the same or similar claims in the present or another patent application.

Interview

Applicants thank Examiner Olson and his Primary Examiner for the telephonic interview with Applicants' attorney and agent on August 27, 2009. The presently submitted claims were discussed during the telephonic interview and it was agreed that the Examiner would consider the non-obviousness of the claims and the unexpected results presented in the Foy declaration.

Claim Rejections – 35 U.S.C. 103

Claims 120-123, and 130-133 remain rejected under 35 U.S.C. §103(a) as being unpatentable over Rossignol *et al.* (U.S. Patent No. 6,184,366) in view of Sanghvi *et al.* (U.S. Patent No. 6,809,195). Specifically, the Office Action states that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to carry out the synthesis carried out by Rossignol *et al.* using a different order of synthetic steps that would result in the claimed intermediates, using any of the methods described by Sanghvi *et al.* to oxidize the phosphorus atom." Applicant respectfully traverses the foregoing rejection for the following reasons.

From the outset, Applicants note, and the Examiner acknowledges at page 3 of the Office Action, that Rossignol *et al.* "does not disclose the specific claimed compounds." Applicants further note that Sanghvi *et al.* fails to cure this deficiency in Rossignol *et al.* in that Sanghvi *et al.* fails to teach or suggest the currently claimed compounds. Indeed, as the Examiner notes at page 3 of the Office Action, "Sanghvi *et al.* discloses a process for preparing oligonucleotides," which Applicants note are distinctly different than the currently claimed liposaccharides.

As a preliminary matter, Applicants submit that an obviousness determination rests on underlying factual inquiries involving: (1) the scope and content of prior art, (2) differences between claims and prior art, (3) the level of ordinary skill in pertinent art, and (4) secondary considerations (*e.g.*, commercial success, long-felt need, etc.). *Graham v. John Deere Co.*, 383 U.S. 1, 17, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). Although, according to the Supreme Court, the

Federal Circuit's "teaching, suggestion or motivation" (TSM) test should not typically be rigidly applied, the Supreme Court confirmed that the TSM test provides helpful insight into the obviousness inquiry. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 127 S.Ct. 1727, 1741, 167 L.Ed.2d 705 (2007). Moreover, the Federal Circuit noted that, even after *KSR*, it still "remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.* (attached herewith as Appendix A and hereinafter "*Takeda*").[1]

Applicants respectfully point out that, in *Takeda*, the Federal Circuit indicated that the case law concerning *prima facie* obviousness of structurally similar compounds is well settled.[2] Specifically, the Court, citing *In re Dillon*, states that "structural similarity between claimed and prior art subject matter, proved by combining references or otherwise, ***where the prior art gives reason or motivation to make the claimed compositions,*** creates a prima facie case of obviousness."[3] However, the court in *Takeda* goes on to clarify this finding by stating that "in addition to structural similarity between the compounds, a prima facie case of obviousness also ***requires*** a showing of 'adequate support ***in the prior art***' for the change in structure…"[4] and further elaborating that "in order to find a prima facie case of unpatentability in cases of structurally similar compounds, ***a showing that the 'prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention' was also required.***"[5]

In *Takeda*, Alphapharm identified a prior art compound ("compound b"), which it asserted was the compound in the prior art that would have been "most promising to modify."[6] Alphapharm then asserted that it would have been obvious to modify compound b by homologation/ring-walking, to generate the compound claimed by Takeda. The court found, firstly, that Alphapharm failed to prove that a person of skill in the art would have chosen compound b for modification, at least partially because of the number of other compounds

[1] *Takeda Chem. Indust. v. Alphapharm Pty., Ltd.* 492 F.3d 1350 (Fed. Cir. 2007).
[2] *Id.*
[3] *Id.* at 1356.
[4] *Id.* (emphasis added), citing *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985).
[5] *Id.* (emphasis added), citing *In re Jones*, 958 F.2d 347 (Fed. Cir. 1992); *In re Dillon* 919 F.2d 688 (Fed. Cir. 1992); *In re Grabiak*, 769 F.2d 729 (Fed. Cir. 1985) and *In re Lalu* 747 F.2d 703 (Fed. Cir. 1984).
[6] *Id.* at 1362-3.

presented in the prior art. Additionally, despite expert testimony that the chemical synthesis of Takeda's compound merely included routine steps in drug optimization, the court found that the process of modifying compounds "was not routine at the time of invention…"[7] Finally, and particularly of note, the court held that, *even if* compound b was the most promising to modify, there is "nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds."[8] Using this rationale, the court found the compound claimed by Takeda to be non-obvious in view of the art presented by Alphapharm.

The Federal Circuit further elucidated their position on obviousness based upon structurally similar compounds in *Procter & Gamble Co. v. Teva Pharma. USA, Inc.* (attached herewith as Appendix B and hereinafter "*Procter & Gamble*").[9] As indicated by the Federal Circuit in *Procter & Gamble*, "[a]n obviousness argument based on structural similarity between claimed and prior art compounds 'clearly depends on a preliminary finding that one of ordinary skill in the art would have selected [the prior art compound] as a lead compound.'"[10] Moreover, according to the Federal Circuit in *Procter &Gamble*, the prior art must identify a reason <u>why</u> a chemist would modify a prior art compound in order to establish a prima facie case of obviousness.[11] Additionally, in considering obviousness, the predictability of the art must also be considered. In *Procter & Gamble,* the Federal Circuit specifically noted the unpredictability of the chemical arts.[12] Thus, an obviousness inquiry ***requires*** a finding that a person having ordinary skill in the art would have had "reason to attempt to make the composition" and "a reasonable expectation of success in doing so."[13]

Also important in an obviousness analysis is the potential number of different options for modification. As discussed in *Procter & Gamble*, when a person of ordinary skill in the art "is

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[7] *Id.* at 1360.
[8] *Id.*
[9] *Procter & Gamble Co. v. Teva Pharma. USA, Inc.,* 566 F.3d 989 (Fed. Cir. 2009).
[10] *Id.* at 994, *citing Takeda*, 492 F.3d at 1359; *see also Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd., 533 F.3d 1353, 1359 (Fed.Cir.2008)* ("post-KSR, a prima facie case of obviousness for a chemical compound still, in general, begins with the reasoned identification of a lead compound" in the prior art).
[11] *Id.* at 995-96, citing *Takeda*, 492 F.3d at 1356-57.
[12] *Id.* at 996. *See, Eisai,* 533 F.3d 1353, 1359 ("To the extent an art is unpredictable, as the chemical arts often are, KSR's focus on [] `identified, predictable solutions' may present a difficult hurdle because potential solutions are less likely to be genuinely predictable.")
[13] *Id.* at 995, *citing PharmaStem Therapeutics, Inc. v. ViaCell, Inc.,* 491 F.3d 1342, 1360 (Fed.Cir.2007).

faced with 'a finite number of identified, predictable solutions' to a problem and pursues 'the known options within his or her technical grasp,' the resulting discovery 'is likely the product not of innovation but of ordinary skill and common sense.'"[14] Alternatively, a person of ordinary skill may be faced with a large number of parameters and choices for modification. In these cases, "researchers can only 'vary all parameters or try each of numerous possible choices until one possibly arrive[s] at a successful result, where the prior art [gives] either no indication of which parameters [are] critical or no direction as to which of many possible choices is likely to be successful.' In such cases, 'courts ***should not succumb to hindsight claims of obviousness***.' Similarly, patents are not barred just because it was obvious 'to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.'"[15]

In *Procter & Gamble,* the district court concluded, and the Federal Circuit agreed, that a compound, 3-pyr-EHDP, was not obvious based upon the disclosure of its positional isomer, 2-pyr-EHDP. The District Court had found that one skilled in the art would not select 2-pyr-EHDP as a lead compound based upon the disclosure in the prior art.[16] The Federal Circuit decided that, even if 2-pyr-EHDP was a lead compound, it would not render 3-pyr-EHDP obvious because a person having ordinary skill in the art would not have had reason to make the *specific* modification out of other possible modifications based on the prior art.[17] Further, the Federal Circuit found that there was no reasonable expectation of success in making modifications to the prior art compound.[18] Similar to *Takeda*, in *Proctor & Gamble*, the court found that there was no credible evidence that the structural modification was routine, despite expert testimony to the contrary.[19]

The facts of *Takeda* and *Procter & Gamble* are analogous to the present case. In the present case, Rossignol *et al.* identified an overall synthetic design, with at least 55 potential intermediates (see, *e.g.*, Rossignol *et al.*, columns 16-22 and 27-50). The Office Action asserts

[14] *Id.* at 996, citing *KSR*, 127 S.Ct. at 1742.
[15] *Id.* at 997, citing *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir.1988), and *In re Kubin,* 561 F.3d 1351 (Fed.Cir.2009). (emphasis added)
[16] *Id.* at 994-95.
[17] *Id.* at 995.
[18] *Id.* at 995-996.
[19] Id. at 997.

that a person of ordinary skill in the art, prior to the present invention, would have chosen specific intermediates in the synthetic scheme to modify in order to generate the compounds of the present invention. However, Applicants respectfully submit that there was no reason prior to the present invention for a person of ordinary skill in the art to choose specific intermediates for potential modification. That is, similar to the facts of *Takeda* and *Procter & Gamble,* there is nothing in Rossignol *et al.* to point to any specific intermediate, much less one which could arguably lead to the claimed compounds, as a lead compound for modification. Without the identification of such a lead compound and particularly in light of the numerous choices presented, the claimed compounds cannot be found obvious in light of the cited art.

Moreover, there is no motivation or suggestion in Rossignol *et al.* as to *why* a person skilled in the art would modify the prior art compound, nor is there any motivation or suggestion for why one skilled in the art would make the *particular* modifications required to arrive at the claimed compounds in view of the prior art. As in *Procter & Gamble,* there are an infinite number of potential modifications that a research chemist could make and nothing in the cited art to suggest the particular modifications necessary to arrive at the claimed invention over other, numerous possibilities. Accordingly, even if there was a reason for a person of ordinary skill in the art to choose a specific intermediate in Rossingnol *et al.* for modification, there is nothing in the prior art (including Sanghvi *et al.*) to suggest making the specific molecular modifications that are necessary to achieve the claimed compounds. Applicants argue that such a teaching in the prior art is ***required,*** according to *Takeda* and *Procter & Gamble*, in order to make a *prima facie* case of obviousness.

Furthermore, and also similar to *Takeda* and *Procter & Gamble*, even if a person of ordinary skill in the art were to choose a specific intermediate from Rossignol *et al.* for modification, ***and*** identify a single modification that would lead to the presently claimed compounds, ***the process of modifying an intermediate such that it maintains its utility is not predictable and certainly not routine***, as clearly evidenced in the Declaration of Dr. Foy submitted on July 2, 2008 (hereinafter "the Foy Declaration"). Briefly, the Foy declaration provides evidence that it was "unexpected at the time the claimed invention was made that this improvement [*i.e.*, synthesis via the claimed intermediates] would lead to a feasible process. For example, when this improvement was suggested to the Process Research department by the

inventor of the above-identified application, the general belief within the department was that ***such an improved process would not be possible***..." (see Foy Declaration, paragraph 6).

In view of the above, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103(a) and reconsideration of claims 120-123 and 130-133.

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Claims 125, 126, 128, 135, 136 and 138 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Rossignol *et al.* (U.S. Patent No. 6,184,366) in view of Greene *et al.* ("Protective Groups in Organic Synthesis). Specifically, the Office Action states that "[i]t would have been obvious to one of ordinary skill in the art at the time of the invention to carry out the synthesis carried out by Rossignol *et al.* using a different order of synthetic steps that would result in the claimed intermediates, using any of the methods described by Greene *et al.* to introduce the allyl carbonate group."

Applicants preliminarily note that neither Rossignol *et al.* nor Greene *et al.* disclose the presently claimed compounds. Applicant respectfully traverses the present rejection for the same reasons as provided above with regard to the rejection over Rossignol *et al.* in view of Sanghvi *et al.*. Specifically, Applicant submits that there was no reason for a person of ordinary skill in the art to choose a specific intermediate in Rossingnol *et al.* for modification, and even if there was, there is nothing in the prior art (including Greene *et al.*) to suggest making the specific molecular modifications that are necessary to achieve the claimed compounds. Applicants argue that such a teaching in the prior art is ***required,*** according to *Takeda* and *Product & Gamble*, in order to make a *prima facie* case of obviousness.

In view of the above, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. §103(a) and reconsideration of claims 125, 126, 128, 135, 136 and 138.

CONCLUSION

In view of the above, Applicants believe the pending application is in condition for allowance. The Examiner is invited to contact the undersigned with questions or comments with regard to the present application.

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Respectfully submitted,

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